BIOTRANSFORMATIONS

THE WORLD BIOTECH REPORT 1987
VOLUME 1 PART 5

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PROCEEDINGS OF THE CONFERENCE HELD AT BIOTECH 87, LONDON, MAY 1987

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Introduction

What is the contribution of biotechnology to the chemical industry, to the product ranges of both large and small companies and to their prospects for profit?

The growing biotransformations marketplace is predicted to reach some $520 million in the USA by 1990. Industrial enzymes, biopolymers, artificial sweeteners and novel applications of existing or modified enzymes in medicine, waste treatment and consumer products all contribute to this market. Evidently biotechnology does have a considerable part to play and this book examines just what that role is.

Biotransformations is one of five books covering Online's Biotech 87 conference. For details of the other four please turn to page 67.

Session Chairman

Dr Peter Baker is Head of Biotechnology Research at the Laboratory of the Government Chemist. He also manages the collaborative BIOTRANS programme and runs the Laboratory's Biotransformations Club.

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The technology challenge for the chemical industry

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The chemical industry in the UK is robust and highly integrated. It spends about 4 percent of its turnover on research and development. Industrial research is mainly conducted by the large companies. The large companies have the capability to conduct research in biotransformation. The concept of 'biotransformation' is important in directing attention to the use of biological catalysts for the conversion of one chemical into another where the chemicals involved are not part of the natural environment of the catalyst. Development of biotransformation must be done against economic objectives, which include the manufacture of chemicals not available by other routes. The technical needs include biological catalyst development, scale up studies, and downstream process development.

Bill Tollett is Managing Director of the consultancy company, Tollett and Company Ltd., and Director of the R&D Clearing House. The R&D Clearing House is a technology bureau established at the request of the UK Chemicals Economic Development Committee with the support of the Chemical Industry Association and the Department of Trade and Industry. Its membership is drawn from a wide spread of chemical companies.

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The UK gives us an example of a West European chemical industry and with Biotech 87 in London it provides an appropriate model for consideration. According to the UK's Chemical Industry Association, it is the country's fifth largest manufacturing industry, producing 9 percent of the gross added value that comes from the nation's manufacturing base. The chemical industry generates a trade surplus of close to £2500 million ($3750 million) per annum. It employs 325,000 people, accounts for about 15 percent of fixed investment in the manufacturing sector in the UK economy and exports 45 percent of its output. The industry spends about 4 percent of its turnover on research and development.

The UK chemical industry is successful. The UK is good at chemistry. It has a structure with ICI as very much the largest UK company in the sector. The chemical interests of Shell, Unilever and BP are at the next level. Companies in specialised parts of the industry such as Courtaulds (fibres), Beecham (pharmaceuticals), BOC (gases) and Glaxo (pharmaceuticals) make up the top eight companies by turnover.

	Turnover, $m	R&D Expenditure, $m	R&D as % of t/o
ICI	15,430	502	3.2
Shell	9,140	205	2.2
Unilever	6,330	365	5.8
BP	3,100	n/a	n/a
Courtaulds	3,100	n/a	n/a
Beecham	2,790	95	3.4
BOC	2,680	n/a	n/a
Glaxo	2,030	130	6.4

(Note that Shell and Unilever are UK/Netherlands companies: the figures presented are for the whole company but refer to external sales and the chemical operations only. The figures for BP refer to external sales and chemical operations: they include Sohio results. BOC results are for chemicals business only.)

There are up to 100 smaller specialised organic chemical companies in the UK chemical industry. They are very good at their job and within their limits they are very innovative, at least as far as development and production are concerned. The industry is a very cooperative one and very interdependent.

Biotechnology and Biotransformation

'Biotransformation' may be defined as the manufacture of chemical products, which would otherwise be made by conventional, non-biological routes, via a biotechnology.

The term 'biotransformation' is more narrowly and specifically defined - we believe with value - as the use of a 'biological catalyst', often a whole organism, for the the conversion of one chemical into another where the chemicals involved are not part of the natural environment of the biological catalyst.

This definition is important in that it turns attention away from well established fermentation processes, such as the manufacture of ethanol or citric acid towards more novel procedures. The definition is not one that would appeal to a tidy mind. It is not rigorous. It does make the point, however, for an industry with a long scientific history, that this is a very new approach to chemical synthesis.

The History

The challenge of biotransformation for the chemical industry has to be seen against a background of the long established skills and expertise of a minerals, coal and oil based chemistry. The science upon which the current chemical industry is based has been 150 years or more in the making. As far as the bulk of the chemical industry is concerned (excluding those engaged in long established processes such as citric acid manufacture or the use of Acetobacter suboxydans for the transformation of D-sorbitol to L-sorbose in vitamin C production), serious consideration of new biotechnology and biotransformation started in the late 1970s with speculation on the production of petroleum analogues from plants, and the use of biotechnology in drug production. By 1980 the European Community was seriously considering a bioengineering programme. In 1981 biotechnology was being seen as a route for expansion by a chemical industry deeply in recession, and magical prospects for the 1990s were being discussed. 1983 saw large amounts of money being raised on Wall Street for biotechnology and tangible investments, such as G.D. Searle's aspartame plant, being built. Biotechnology continued to be exciting in 1984 and into 1985 but since then and especially in 1986 superficial commercial excitement in biotechnology has evaporated as easy profits did not materialise. Indeed in 1985/86 we saw a regrouping of biotechnology interests among the chemical companies internationally, with those who had their fingers burned, salvaging what they could, in many cases by selling their biotechnology assets at a low price to other companies who were by then seeking a position. Behind the superficial commercial waxing and waning, however, there remains a continuing research interest. In most cases it is a research interest which has about 10 years of history.

The Motivation

The fundamental driving force for any new technology in a market based industry is economic. There are other subjective driving forces, however. The chemical industry its tired of being pilloried as a despoiller of things natural and would be very happy to have some protection from the accusing finger and the effluent problems, the air pollution, and the slag heaps. Love Canal, Bhopal, Lake Erie, and the River Rhine may not be UK problems but they certainly influence UK thinking.

The ultimate advantages of developing biotransformations are likely to lie not only in the possibility of making conventional products better, but also, indeed more probably, in being able to make new materials for pharmaceutical, veterinary and pesticide use of acceptable quality at all.

For example the market pull and the regulation push in the life sciences industries are towards the use of small quantities of pure highly active isomers rather than the broadscale use of racemic mixtures. Biotechnology has intrinsic advantages in the preparation of optically active materials.

The Pressures

The chemical industry is an enabling industry. It is the materials supplier to all the other manufacturing industries. Its role with respect to biotechnology is as a user of the skill. Biotechnology in general and biotransformation in particular are part of a range of skills available, or potentially available, for the chemical industry to use in fulfilling its role. The choice of biotechnology as a route for chemicals manufacturing depends on availability of a developed process and plant, cost and accessibility of raw materials, acceptability of the process and product in consumer, environmental and legislative terms, process reliability, and most importantly, costs of manufacture in relation to alternative routes.

All these considerations are interdependent. Many of them have a political dimension. Within the European Community tariffs and agricultural policy distort the price of grain and sugar in relation to the world free market price. The effects of the manufacturing environment in which a chemical industry operates show in, for example, the production of ethanol in the UK in contrast with the production in Brazil or India. In the UK, with a highly developed oil based commodity chemical industry, and a policy of supporting high prices for agricultural products, we estimate that production of ethanol for industrial purposes has been thus:-

UK Industrial Ethanol Production

('000 tonnes)

	1980	1981	1982	1983	1984	1985
Chemical Synthesis	153	163	178	221	231	221
Biotechnology	6	7	7	6	7	7
Total	159	170	185	227	238	228

In other territories, with ready availability of cheap raw materials and an economy short of oil and dollars, the balance of ethanol production is entirely different. (In Brazil, the annual production of ethanol by biotechnology is close to 4,500,000 tpa and in India it is close to 400,000 tpa.)

The competition between conventional manufacture and biotransformation is illustrated by the manufacture of steroids. Conventional introduction of an hydroxyl group at the 11 position of a steroid structure is extremely difficult.

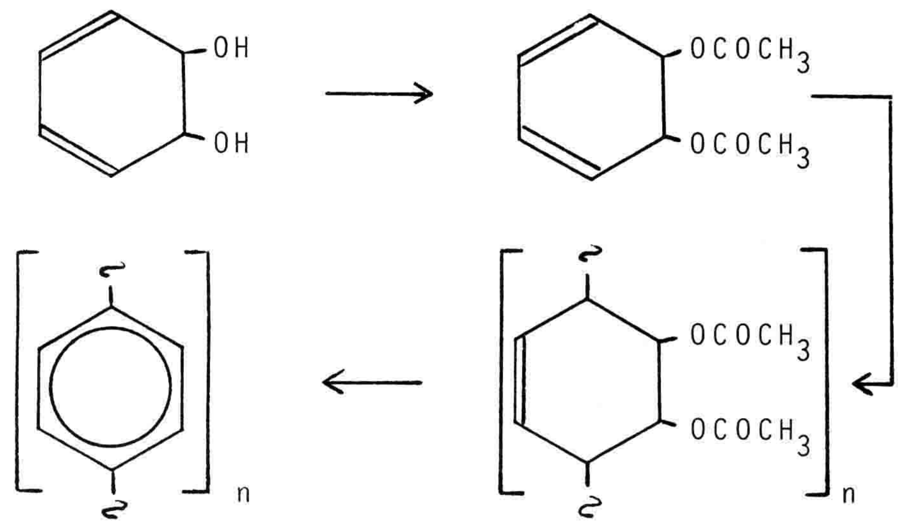
Upjohn scooped the pool by commercialising a microbial method. Nevertheless new research work continues on chemical synthesis routes. (D. Neville Jones, University of Sheffield.) There is in fact a view in the chemical industry that biotransformation can be used to determine the feasibility of a process and the synthesis route: synthetic organic chemistry can then define a cost effective way of effecting the manufacture.

ICI has achieved something of a breakthrough in biotransformation with the process for benzene cis glycol. One of the key considerations behind the ICI work was the wish to achieve rapid scale up and meet defined economic targets.

ICI has adopted a leading position in aromatic polymer development. Polyphenylene (B) is one such. A route to the manufacture of polyphenylene is from cis-1,2-dihydroxycyclohexa-3,5-diene (A) which has the trivial name, benzene-cis-glycol. The polymerisation may be represented as in the diagram:-

A

B



Published large scale conventional synthesis of benzene-cis-glyol is multi-stage and low yielding. Hence ICI turned to enzymic routes. Benzene-cis-glycol is an intermediate in benzene metabolism in some bacteria. In particular the dioxygenase enzyme from a Pseudomonas species has been shown to convert benzene and indeed substituted aromatics to cis-2,3-dihydroxy compounds.

A highly efficient strain of Pseudomonas putida was developed by genetic modification of one originally isolated in the vicinity of an ICI chemical plant. The procedure used resting whole cells for the transformation stage with cofactor regeneration by co-oxidation of suitable cheap energy sources such as ethanol or glucose. ICI has operated the system at up to a 1000 litre scale giving a production of multi-kilogram amounts of various cis-glycols. Catalytic lifetimes are short but high yields on benzene and energy consumption are reported. Concentrations of product in tens of kilograms per cubic metre have been reported.

The Technical Needs

The use of biological catalysts in chemical synthesis, and the development of routes to both existing and new stereospecific molecules are the topics exciting attention.

The technology challenge for the chemical industry from biotransformation is on a number of fronts - separations processes, reactor design, co-factor recycling and lack of robustness of biological catalysts. (Biological catalysts lack resistance to extremes of pH and heat, and they may show substrate and product inhibition.) Biological catalysts have other disadvantages: there are difficulties in using them in low water environments or with materials of limited solubility. Process scale-up is also creating problems.

The major technical challenges are not in materials of construction, toxic hazards (except to the catalysts) or the other areas about which concern was expressed at the end of the 1970s.

Who can Respond to the Challenge, and How?

The parts of the challenge are:-

a The inception and proving of the new idea - the 'research',

b The further work on the proven idea to the definition of a viable process and an acceptable product - the 'development', and

c The continuing maintenance of the product and process technology.

A few companies can do step a. A larger number can do steps b and c.

ICI has the wherewithal to do biotransformation research. Shell has a new development with Gist Brocades. Unilever has major interests in biotechnology. The large companies have the resources.

However, the bulk of UK chemical companies have no biologists, and no history of biological science beyond the control of a biological effluent plant and some testing for sterility. This is totally inhibiting where the establishing of biotransformation is concerned.

Outside the large companies the major resource for biotechnology research in general and biotransformation research in particular lies with the universities and polytechnics, the research associations, government research establishments and research contractors.

The Real Problem

Despite the foregoing, the real problem is not in fact the technology challenge. The real problem is the time span and the money. Research on biotransformation started now might yield commercial profit in 10-20 years time. The annual financial reporting cycle of commercial companies has meant that investment in R&D has come to be seen by some as a drain on this years' profits rather than the originator of the future's profits. This is the problem the UK chemical industry must address - for new development in general and biotransformation in particular.

The impact of biotechnology on the chemical industry: a US viewpoint

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There has been rapid development recently in some of the newer technologies such as protein engineering, high level secretion systems and pathway engineering. This will reduce or eliminate some of the technical obstacles to the application of biotechnology to the production of chemicals. Indeed these developments are already being translated into commercial applications in the chemical industry.

Dr. MacQuitty is head of the Commercial Development group at Genencor and also oversees patent, legal and public relations activities. He has prior experience at Genentech, Exxon Chemicals and the Boston Consulting Group. He has an MBA from Stanford and a Ph.D. in Chemistry.

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